

PATENT
Patent No. 6,936,584 B1
Serial No. 09/622,104
Amylin Docket No.: 256/153 US

THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No.: US 6,936,584 B1

Issue Date: August 30, 2005

Art Unit: 1639

Applicants: Nigel R.A. Beeley et al.

Examiner: B. Celsa

Serial No.: 09/622,104

Filed: July 16, 2001

Title: Novel Mixed Amylin Activity Compounds

REQUEST FOR CERTIFICATE OF CORRECTION

Attention Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate
NOV 30 2005
of Correction

Sir:

Applicants hereby request a Certificate of Correction under 37 C.F.R. § 1.322 regarding U.S. Patent No. 6,936,584 B1, issued August 30, 2005. The following documents are enclosed for your review and consideration:

1. Certificate of Correction - 1 page
2. Copy of USPTO Response to Rule 312 Communication - 2 pages
3. Pages from subject patent highlighting corrections to be made and corrections to be inserted - 2 pages

CERTIFICATE OF MAILING
(37 C.F.R. §1.10)

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage in an envelope addressed to :Attention Certificate of Correction, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

November 21, 2005
Date of Deposit

Amanda J. Dahlerson
Name of Person Mailing Paper
Amanda J. Dahlerson
Signature of Person Mailing Paper

NOV 30 2005

In support of Applicants request to correct the 35 USC § 371(c), (1), (2), (4) date, the Patent Office in their Response to Rule 312 Communication dated July 1, 2005 (copy attached), accepted Applicants request for a corrected filing receipt indicating the correct filing date under 35 USC § 371(c), (1), (2), (4) as July 16, 2001. Therefore, Jul. 17, 2001 should be removed and Jul. 16, 2001 inserted.

Additionally, in support of Applicants request to correct claim 19, the Patent Office allowed claims 1-25 in the Notice of Allowability mailed January 19, 2005. Claim 19, as originally filed, indicated dependency on claims 1 to 18 and remained as the original claim throughout the prosecution of this patent. Therefore, in claim 19 the number 8 should be removed and 18 inserted as originally filed.

Applicants believe that the errors are due to mistakes on the part of the Patent Office and therefore do not believe any fees are due with this submission. However, if any fees should become due in connection with this submission the Commissioner is hereby authorized to charge any additional fees or credit any overpayment to Applicant's Deposit Account No. 010535. A duplicate of this sheet is enclosed for this purpose.

Respectfully submitted,

AMYLIN PHARMACEUTICALS, INC.

Dated: 21 November 2005

By: Karen R. Zachow
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UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

Page 1 of 1

PATENT NO. : US 6,936,584

APPLICATION NO.: 09/622,104

ISSUE DATE : August 30, 2005

INVENTOR(S) : Nigel R.A. Beeley, Kathryn Prickett, Kevin Beaumont

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

1. Page 1 (cover page), column 1, section labeled (86) third line, "Jul. 17, 2001" should be changed to --Jul.16, 2001--.
2. Column 46, claim 19, line 7, "8" should be changed to --18--.

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Amylin Pharmaceuticals, Inc. Attn: Karen R. Zachow
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San Diego, CA 92121

This collection of information is required by 37 CFR 1.322, 1.323, and 1.324. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1.0 hour to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: **Attention Certificate of Corrections Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

NOV 30 2005



US006936584B1

(12) **United States Patent**
Beeley et al.(10) **Patent No.: US 6,936,584 B1**
(45) **Date of Patent: Aug. 30, 2005**(54) **MIXED AMYLIN ACTIVITY COMPOUNDS**(75) **Inventors:** Nigel R. A. Beeley, Solana Beach, CA (US); Kathryn Prickett, San Diego, CA (US); Kevin Beaumont, San Diego, CA (US)(73) **Assignee:** Amylin Pharmaceuticals, Inc., San Diego, CA (US)(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.(21) **Appl. No.:** 09/622,104(22) **PCT Filed:** Feb. 5, 1999(86) **PCT No.:** PCT/US99/02603

§ 371 (c)(1),

(2), (4) **Date:** Jul. 17, 2001 Jul. 16, 2001(87) **PCT Pub. No.:** WO99/40928**PCT Pub. Date:** Aug. 19, 1999**Related U.S. Application Data**(60) **Provisional application No.** 60/074,746, filed on Feb. 13, 1998.(51) **Int. Cl.⁷** A61K 37/02; C07K 7/10(52) **U.S. Cl.** 514/12; 514/866; 530/324(58) **Field of Search** 530/324; 514/12, 514/866(56) **References Cited****U.S. PATENT DOCUMENTS**

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(Continued)

Primary Examiner—Bennett Celsa(74) **Attorney, Agent, or Firm**—Arnold & Porter LLP

(57)

ABSTRACT

Compounds which inhibit certain activities of amylin but which also act as amylin agonists with respect to other amylin activities are disclosed. Such compounds are useful in treating disturbances in fuel metabolism in mammals, including but not limited to, diabetes, mellitus, including Type I diabetes and Type II diabetes, impaired glucose tolerance, insulin resistance and Syndrome X. The present invention also relates to methods of treating Type I diabetes, beneficially regulating gastrointestinal motility, treating impaired glucose tolerance, treating postprandial hyperglycemia, treating obesity and treating Syndrome X, comprising administration of a therapeutically effective amount of certain compounds, as described herein.

-continued

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 <223> OTHER INFORMATION: Xaa stands for NH₂

<400> SEQUENCE: 31

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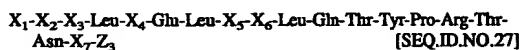
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 <21> NAME/KEY: Amidation
 <222> LOCATION: (7)
 <223> OTHER INFORMATION: Xaa stands for NH₂

<400> SEQUENCE: 32

Val Gly Ser Gly Thr Pro Xaa
 1 5

We claim:

1. A compound of the formula:



wherein:

(a) X₁ is

(i) a group of two amino acid residues selected from the group consisting of Leu-Leu, Val-Leu, Ile-Leu, tert-Leu-Leu, Nle-Leu, and Ala-Thr, and N-acylated derivatives thereof; or

(ii) the group Z₁-Ser-Thr-Z₂-Val-Leu [SEQ.ID.NO. 28] wherein Z₁ is an amino acid residue selected from the group consisting of Leu, Val, Ile, tert-Leu, Nva, Abu, and Nle or an N-acylated derivative thereof or Z₁ is an alkanoyl group; and Z₂ is an amino acid residue selected from the group consisting of Ala, Ser, Cys, and Thr;

(b) X₂ is an amino acid residue selected from the group consisting of Gly, Glu, Asn or Aib;

(c) X₃ is an amino acid residue selected from the group consisting of Arg, Orn, Lys and ε-amidated derivatives thereof;

(d) X₄ is a group of two amino acid residues selected from the group consisting of Ser-Gln, Thr-Gln, Ala-Asn and Thr-Asn;

(e) X₅ is an amino acid residue selected from the group consisting of His, Aib, Ile, Leu and Val;

(f) X₆ is an amino acid residue selected from the group consisting of Arg, Orn and Lys and ε-amidated derivatives thereof;

(g) X₇ is a group having 6 amino acid residues selected from the group consisting of

(i) Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 29];

(ii) Thr-Gly-Ser-Gly-Thr-Pro [SEQ.ID.NO. 30];

(iii) Val-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 31];

(iv) Val-Gly-Ser-Gly-Thr-Pro [SEQ.ID.NO. 32]; and

(h) Z₃ is OH or NH₂;

with the proviso that the compound does not have the formula of any of SEQ. ID. NOS. 14 to 26; and pharmaceutically acceptable salts thereof.

25 2. A compound according to claim 1 wherein Z₃ is NH₂.

3. A compound according to claim 1 wherein X₂ is Gly.

4. A compound according to claim 3 wherein X₅ is His or Aib.

5. A compound according to claim 4 wherein X₄ is Ser-Gln.

6. A compound according to claim 5 wherein X₇ is Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 29] or Thr-Gly-Ser-Gly-Thr-Pro-NH₂ [SEQ.ID.NO. 30].

7. A compound according to claim 6 wherein X₁ is Z₁-Ser-Thr-Z₂-Val-Leu [SEQ.ID.NO.28].

8. A compound according to claim 7 wherein X₃ and X₆ are ε-amidated with a carboxylic acid having 1 to 8 carbon atoms.

9. A compound according to claim 1 wherein Z₁ is an alkanoyl group having 1 to about 10 carbon atoms or Leu.

10. A compound according to claim 9 wherein Z₂ is Ala or Cys.

11. A compound according to claim 10 wherein Z₁ is an alkanoyl group.

12. A compound according to claim 11 wherein X₃ and X₆ are formamidated or acetamidated.

13. A compound according to claim 12 wherein Z₂ is Ala.

14. A compound according to claim 13 wherein X₃ and X₆ are Lys(For).

15. A compound according to claim 14 wherein Z₁ is 4-methylpentanoyl.

16. A compound according to claim 1 which has an amino acid sequence selected from the group consisting of:

Leu-Ser-Thr-Cys-Val-Leu-Gly-Arg-Leu-Ser-Gln-Gln-Leu-His-Arg-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 1];

4-methylpentanoyl-Ser-Thr-Ala-Val-Leu-Aib-Lys(For)-Leu-Ser-Gln-Gln-Leu-Aib-Lys(For)-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro [SEQ.ID.NO. 2];

Ac-Leu-Ser-Thr-Ser-Val-Leu-Gly-Arg-Leu-Ser-Gln-Gln-Leu-His-Arg-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 3];

Leu-Ser-Thr-Ala-Val-Leu-Gly-Arg-Leu-Ser-Gln-Gln-Leu-His-Arg-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 4];

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Leu-Ser-Thr-Ser-Val-Leu-Gly-Arg-Leu-Ser-Gln-Glu-Leu-His-Arg-
Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-
Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 5];

Ac-Leu-Ser-Thr-Ala-Val-Leu-Gly-Arg-Leu-Ser-Gln-Glu-Leu-His-
Arg-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Asn-Thr-
Tyr [SEQ.ID.NO. 6];

Ac-Leu-Ser-Thr-Cys-Val-Leu-Gly-Arg-Leu-Ser-Gln-Glu-Leu-His-
Arg-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Asn-Thr-
Tyr [SEQ.ID.NO. 7];

Val-Leu-Aib-Lys(For)-Leu-Ser-Gln-Glu-Leu-Aib-Lys(For)-Leu-Gln-
Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-
Asn-Thr-Tyr [SEQ.ID.NO. 8];

Ac-Val-Leu-Aib-Lys(For)-Leu-Ser-Gln-Glu-Leu-Aib-Lys(For)-Leu-
Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-
Ser-Asn-Thr-Tyr [SEQ.ID.NO. 9];

4-methylpentanoyl-Ser-Thr-Ala-Val-Leu-Aib-Lys(For)-Leu-Ser-
Gln-Glu-Leu-Aib-Lys(For)-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-
Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 10];

4-methylpentanoyl-Ser-Thr-Cys-Val-Leu-Aib-Lys(For)-Leu-Ser-
Gln-Glu-Leu-Aib-Lys(For)-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-
Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 11];

Ala-Thr-Aib-Lys(For)-Leu-Ala-Asn-Glu-Leu-Aib-Lys(For)-Leu-
Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-
Ser-Asn-Thr-Tyr [SEQ.ID.NO. 12];

and

Ac-Ala-Thr-Aib-Lys(For)-Leu-Ala-Asn-Glu-Leu-Aib-Lys(For)-
Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-
Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 13].

17. The compound Leu-Ser-Thr-Cys-Val-Leu-Gly-Arg-
Leu-Ser-Gln-Glu-Leu-His-Arg-Leu-Gln-Thr-Tyr-Pro-Arg-
Thr-Asn-Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 1].

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18. The compound 4-methylpentanoyl-Ser-Thr-Ala-Val-
Leu-Aib-Lys(For)-Leu-Ser-Gln-Glu-Leu-Aib-Lys(For)-
Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-
Pro [SEQ.ID.NO. 2].

19. A composition comprising a compound of any of
claims 1 to 8 in a pharmaceutically acceptable carrier.

20. A method of treating diabetes in a subject in need of
treatment which comprises administering to said subject a
therapeutically effective amount of a compound of any of
claim 1, 2, 15, 16, 17 or 18.

21. A method according to claim 20 wherein said diabetes
is type I diabetes.

22. A method according to claim 20 wherein said diabetes
is type II diabetes.

23. A method of beneficially regulating gastrointestinal
motility in a subject comprising administering to said sub-
ject a therapeutically effective amount of a compound of any
of claim 1, 2, 15, 16, 17 or 18.

24. A method according to claim 23 wherein said benefi-
cial regulation of gastrointestinal motility comprises delay-
ing gastric emptying.

25. A method of treating a disorder selected from the
group consisting of: impaired glucose tolerance; postpran-
dial hyperglycemia; obesity; and Syndrome x; in a subject in
need of treatment which comprises administering to said
subject a therapeutically effective amount of a compound of
any of claim 1, 2, 15, 16, 17 or 18.

* * * * *



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/622,104	07/17/2001	Nigel R.A. Beeley	030639.0057.US	8378
44638	7590	07/01/2005	EXAMINER	
ARNOLD & PORTER LLP (18528) 555 TWELFTH ST, NW WASHINGTON, DC 20004			CELSA, BENNETT M	
			ART UNIT	PAPER NUMBER
			1639	

DATE MAILED: 07/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

NOV 30 2005

Response to Rule 312 Communication	Application No.	Applicant(s)	
	09/622,104	BEELEY ET AL.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

1. ☒ The amendment filed on 18 April 2005 under 37 CFR 1.312 has been considered, and has been:

a) ☒ entered.

b) ☐ entered as directed to matters of form not affecting the scope of the invention.

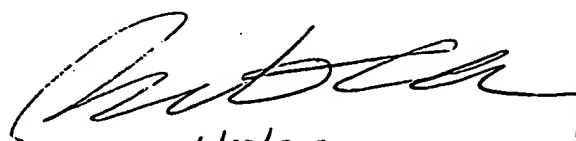
c) ☐ disapproved because the amendment was filed after the payment of the issue fee.

Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

d) ☐ disapproved. See explanation below.

e) ☐ entered in part. See explanation below.

The Bibliographic Sheet information has been revised to indicate 7/16/01 filing date of present application and Office of Initial Patent Examination (OIPE) has been notified as to corrected filing receipt.



6/23/05
Bennett Celsa
Primary Examiner
Art Unit: 1639